

Pancreatic Insufficiency, Digestive Enzyme Supplementation and Postnatal Growth in Preterm Babies

Allan C Jenkinson¹, Narendra Aladangady^{1,2}, Sven Wellmann³, Simon Eaton⁴, Christoph Bühner⁵ & *Paul Fleming^{1,2}, *Charles Roeher^{6,7}

¹ Department of Neonatology, Homerton Healthcare NHS Foundation Trust, London, United Kingdom

² Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

³ Department of Neonatology, University Children's Hospital Regensburg (KUNO), Hospital St. Hedwig of the Order of St. John, University of Regensburg, Regensburg, Germany

⁴ UCL Great Ormond Street Institute of Child Health, University College London, London, UK

⁵ Department of Neonatology, Charité – Universitätsmedizin Berlin, Berlin, Germany

⁶ National Perinatal Epidemiology Unit Clinical Trials Unit, Oxford Population Health, Medical Sciences Division, University of Oxford, Oxford, UK

⁷ Faculty of Health Sciences, University of Bristol, Newborn Services, Southmead Hospital, North Bristol Trust, Bristol, UK

*Denotes equal author contribution

Corresponding author: Dr. Allan Jenkinson

Email: allan.jenkinson@kcl.ac.uk

Postal address: Homerton Healthcare NHS Foundation Trust, Homerton Row, London E9 6SR

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Abstract:

Optimising postnatal growth facilitates better long term neonatal neurodevelopmental outcomes. Early postnatal growth is often hindered by a variety of factors unique to the extrauterine environment and digestive immaturity both contributing to reduced enteral feed tolerance during the first few days and weeks after birth.

Preterm infants display varying levels of pancreatic insufficiency that are related to gestational age and providing digestive enzyme supplementation, may be one way in which to improve postnatal growth in enterally fed preterm babies.

In this review, we explore which exocrine pancreatic enzymes are deficient in preterm babies, the methods by which exocrine pancreatic function is measured, potential avenues by which digestive enzyme replacement might improve postnatal growth failure and which babies might benefit most from this intervention.

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Introduction

Early postnatal growth is essential for improved long-term neurodevelopmental outcomes and survival in preterm babies [1, 2] but may be hindered by high energy expenditure, an immature gastrointestinal tract and increased nutrient losses [2, 3]. As a result, few preterm babies grow along the same trajectory that their birth centile would have predicted [4].

Adequate nutrition in preterm infants is reliant upon both nutrient supply and assimilation. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) provide up-to-date recommendations on optimum nutrient requirements for preterm babies [1].

While it is well established that adequate nutrient supply is essential for growth, attention has recently turned to the role of preterm assimilation in augmenting nutritional gains. One area of emerging interest within this field, is the role of accessory glands, and in particular the exocrine function of the pancreas.

Exocrine pancreatic insufficiency leading to malnutrition is well described in children and young adults with cystic fibrosis (CF) [5]. More recently, exocrine pancreatic insufficiencies have been described for term and preterm infants [6] which has led to further research on pancreatic exocrine dysfunction and the effect of pancreatic enzyme replacement therapy in preterm babies with faltering growth.

The aim of this review is to summarise current understanding of functional immaturity of the exocrine pancreas in preterm babies and to review the methods by which pancreatic exocrine function is evaluated. We explore the use of exogenous pancreatic enzymes in studies aimed at optimising nutrient digestion and describe how pancreatic replacement therapy might help specific groups of preterm infants with compromised growth.

Historical recognition of pancreatic functional immaturity in preterm babies

The first histological examinations of the pancreas describing maturational differences in pancreatic exocrine function between term and preterm babies date back to the 1940s [7]. The ontogeny of common pancreatic enzymes has been well described and summarised in a recent review by Mehta et al. [8]. While enzyme activity is detectable in human foetal pancreatic tissue from before 20 weeks' gestation, each enzyme appears and develops individually over time [9]. As a result, extremely preterm infants may have lower levels of pancreatic enzymes at birth, as compared to late preterm or term infants [10]. It has been postulated that this insufficiency may be targeted to achieve better postnatal growth.

Measuring exocrine pancreatic function

Much like our understanding of the functional development of the pancreas, functional testing methods have evolved considerably over the last several years. Original invasive sampling collection has been replaced by less invasive breath, serum and stool measurements of pancreatic enzymes, and products of digestion [11].

Indirect tests of pancreatic function are categorised into: (1) measuring products of pancreatic enzyme activity in urine or stool (pancreolauryl test); (2) analysing undigested and unabsorbed food components in stool (faecal fat excretion, efficiency of fat/nitrogen absorption) or the analysis of oxidation products of digested and absorbed fat in expired air (breath tests); or (3) measuring pancreatic enzymes in serum (amylase, lipase, trypsinogen, elastase-1) or stool (chymotrypsin, lipase, elastase-1) [12]. While these tests are considered less invasive, less expensive and less time consuming, their application in paediatrics practice poses some practical challenges. [12].

Measurement of faecal elastase 1 (FE1) is the most convenient marker of exocrine pancreatic insufficiency [13]. Elastase shares a common development pathway with other proteolytic enzymes, and as such, low levels observed in patients with pancreatic insufficiency parallel those of other proteolytic enzymes [14]. Elastase is itself relatively resistant to digestion so that faecal elastase is thought to reflect pancreatic secretion.

Multiple studies have shown that measurement of FE1 levels is sensitive in children [13, 15, 16]. FE1 concentrations of >200 µg/g are considered to reflect normal pancreatic function [17] with FE1 concentrations <200 µg/g indicating a degree of pancreatic insufficiency.

Low FE1 levels are associated with impaired catch up growth in infants born at <28 weeks gestation [10]. It is therefore hypothesised that by supplementing pancreatic enzymes, this might counteract growth failure attributable to pancreatic insufficiency.

Digestive enzyme supplementation in preterm infants

The use of digestive enzyme replacement treatment (DERT) in preterm infants is based upon the historical use of DERT in infants and children with CF [18] where it has been shown to be essential for nutrient digestion and absorption and for growth and development [18, 19]. Three types of DERT have been evaluated in preterm babies, recombinant human bile salt-stimulated lipase (rhBSSL), porcine pancreatic enzymes (formulated with an acid-resistant coat), and digestive enzymes (lipase and protease) of microbial origin.

In infants, digestion of triglycerides is achieved through the action of gastric lipase, pancreatic lipase, and bile salt-stimulated lipase (BSSL) [20]. Bile salt-stimulated lipase is an endogenous pancreatic enzyme, as well as being found abundantly in breast milk [21]. BSSL in breast milk compensates for the limited capacity of infant pancreatic enzymes during the first months after birth. Babies receiving donor breast milk however, do not have BSSL supplemented in the milk, as BSSL is denatured in the pasteurisation of donor milk and ultimately deactivated [22]. As a result, preterm infants receiving donor or formula milk have limited fat digestion capacity. It has been suggested that recombinant human BSSL (rhBSSL) may play a role in fat digestion in these infants. Recombinant human BSSL (rhBSSL) is produced from hamster ovary cells [23], transgenic mice [24, 25] and cows [26].

Porcine pancreatic extracts [27] containing lipase, protease and amylase have also been shown to benefit patients with exocrine pancreatic insufficiency [28]. Whereas BSSL only improves fat digestion, pancreatic extracts may additionally aid carbohydrate and protein digestion. First sold as Kreon® (Abbott Laboratories GmbH, Hannover, Germany) there are now numerous generic formulations on the market [29].

As pancreatic enzymes are rapidly inactivated by pepsin in the acidic environment of the stomach, they are coated with an acid-resistant surface that releases the enzymes only after passage to the alkaline lumen of the duodenum [30]. The need for acid-resistant coating can be obviated by microbial enzymes (lipase, protease, and amylase) from *Rhizopus oryzae* and *Aspergillus oryzae* that are intrinsically acid-resistant. A mixture of these enzymes (Nortase®, Repha GmbH, Langenhagen, Germany) is licensed in Germany to treat exocrine pancreatic insufficiency without patient age limit [31].

Evaluation of studies using DERT in preterm infants

Several studies using purified pancreatic enzymes, rhBSSL and microbial digestive enzymes have been conducted in preterm babies to evaluate their effect on improved growth. One double-blinded phase 2 study investigating rhBSSL supplementation in preterm infants receiving pasteurised human milk or formula showed that one week of treatment with rhBSSL significantly improved growth and long-chain polyunsaturated fatty acid absorption compared to infants in the placebo group [23]. In particular, rhBSSL treatment significantly improved mean growth velocity compared with placebo (mean 16.86g/kg/day vs 13.93g/kg/day, $P = <0.001$) and significantly decreased the risk of suboptimal growth ($<15\text{g/kg/day}$) (30% vs 52%, $P=0.004$). However, these positive results did not

translate in a follow on phase 3 multicentre, prospective, randomised, double blind trial which disappointingly showed no effects on growth velocity (16.77 vs. 16.56 g/kg/day, 95% CI [-0.40; 0.83]) or Bayley neurodevelopmental scores at 12 months of corrected age [32].

Importantly though, a subgroup analysis, revealed a significantly higher growth velocity in infants small-for-gestational age (SGA) in the rhBSSL group compared to the placebo group. Of note, whilst higher proportions of infections, gastrointestinal intolerance, and NEC were initially seen in the rhBSSL treated group, this imbalance equalized during the follow-up period. The study was likely underpowered to reflect a true association with NEC.

A further retrospective case-control study compared 26 preterm infants receiving pancreatic enzymes (<32weeks, <1500g) to matched controls (N=52) [33]. Infants were selected for supplementation if they showed postnatal growth failure or growth restriction (defined as loss of >0.5 weight SD score (SDS) compared with birthweight SDS without trend to resume birth trajectories) despite intensified enteral nutritional support. The group reported that weight gain increased in the supplemented group from 13.6 (4.2–22.9) g/kg/day in the week before to 19.0 (10.9–29.1) g/kg/day in the week after commencing pancreatic enzyme supplementation. This was significant when compared to weight gain in the control group.

Another study looked at supplementation of digestive enzymes of microbial origin in a group of preterm infants with clinically and biochemically diagnosed pancreatic insufficiency (FE1 levels <200 µg/g) [34]. Among participants in this study, digestive enzyme replacement was associated with a statistically significant increased weight gain and head circumference growth [34].

Challenges with DERT Formulation

There is limited guidance on optimum dosing regimens [18] for DERT in babies despite extensive experience over many years of their use in the management of newborn babies with CF [35-37]. A recent systematic review by Ng et al. looked at efficacy (fat absorption) and effectiveness (nutritional status, lung function and quality of life) of DERT regimes in all patient cohorts but could not determine whether higher dosing regimens of DERT were more effective than lower dosing regimens of DERT [38]. Furthermore, they were they unable to define the optimum timing, in relation to a meal, for DERT supplementation [38]

Evidence on the most effective preparation of DERT to use in both infants and adults is also limited [19]. In their Cochrane review, Somaraju et al. evaluated 14 trials (in children and adults) [19] of different enteric and non-enteric coated preparations with different formulations but could not perform a meta-analysis of the data, due to heterogeneity of the products used.

As a result, although DERT is an established treatment strategy in infants and children with CF, there is limited evidence on optimum formulations, preparations, dosing and duration of treatment making it difficult to extrapolate DERT treatment strategies for other groups such as preterm and/or very low birth weight infants.

A further challenge with using DERT in preterm infants relates to issues with available formulations. Non-enteric coated formulations are susceptible to acid breakdown in the stomach and are not clinically useful [39]. A recent advance in enzyme administration has been reported, describing a novel method of crushing enzyme beads and adding them directly to enteral formula delivered by fine bore (<10 Fr) nasogastric tubes, in a very low birth weight preterm infant with CF[40]. Another novel delivery method includes an in-line digestive cartridge containing immobilized lipase, which digests fat as the enteral feed passes through the cartridge. This product is currently only available in North America, and has not been trialled in preterm infants [41].

Conclusion and Recommendations

Developmental transient immaturity of pancreatic exocrine function is common in extremely preterm babies. It appears to be more pronounced in babies with evidence of intrauterine growth restriction and may contribute to growth failure during the first six months after birth. Modern testing methods to diagnose pancreatic insufficiency, such as stool elastase measurements, are known to be simple, non-invasive and accurate and represent an easy method for pancreatic assessment in preterm babies.

While it has been postulated that digestive enzyme replacement therapy may benefit babies with evidence of postnatal growth failure and pancreatic exocrine insufficiency, the available evidence does not presently support the use of digestive enzyme supplementation in preterm infants including those born small for gestational age.

Future studies should comprehensively evaluate FE1 levels in preterm babies of varying gestations and validate its role in identifying babies with evidence of pancreatic insufficiency. Large adequately powered randomised controlled trials to evaluate whether DERT supplementation improves faltering growth in preterm babies, especially focusing on SGA infants, may be justified.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Author contributions

AJ – literature review, initial draft manuscript

NA – expert review of manuscript

SW – expert review of manuscript

SE – expert review of manuscript

CB – expert review of manuscript

PF – conceptualisation, review of manuscript and final approval

CR – conceptualisation, review of manuscript and final approval

References

1. Embleton, N.D., et al., *Enteral Nutrition in Preterm Infants (2022): A Position Paper From the ESPGHAN Committee on Nutrition and Invited Experts*. J Pediatr Gastroenterol Nutr, 2023. **76**(2): p. 248-268.
2. Giuliani, F., et al., *Monitoring postnatal growth of preterm infants: present and future*. Am J Clin Nutr, 2016. **103**(2): p. 635s-47s.
3. Henderickx, J.G.E., et al., *Maturation of the preterm gastrointestinal tract can be defined by host and microbial markers for digestion and barrier defense*. Scientific Reports, 2021. **11**(1): p. 12808.
4. Bendor-Samuel, O.M., et al., *A Comparison of UK Preterm Anthropometric Charts and INTERGROWTH-21st: Is It Time to Change Growth Charts?* Neonatology, 2020. **117**(3): p. 300-307.
5. Singh, V.K. and S.J. Schwarzenberg, *Pancreatic insufficiency in Cystic Fibrosis*. Journal of Cystic Fibrosis, 2017. **16**: p. S70-S78.

6. Struyvenberg, M.R., C.R. Martin, and S.D. Freedman, *Practical guide to exocrine pancreatic insufficiency - Breaking the myths*. BMC Med, 2017. **15**(1): p. 29.
7. Werner, B., *Peptic and Tryptic Capacity of the Digestive Glands in Newborns: From the Sachs' Hospital for Children and The Chemistry Department II of the Caroline Institute, Stockholm. A Comparison Between Premature and Full-term Infants.*(Diss. Stockholm 1948.)(Translated by Erica Odelberg.). 1948: Almqvist & Wiksell.
8. Mehta, V., et al., *Development of the human pancreas and its exocrine function*. Front Pediatr, 2022. **10**: p. 909648.
9. McClean, P. and L.T. Weaver, *Ontogeny of human pancreatic exocrine function*. Archives of disease in childhood, 1993. **68**(1 Spec No): p. 62-65.
10. Münch, A., L. Garten, and C. Bühner, *Protracted maturation of pancreatic-specific elastase 1 excretion in preterm infants of extremely low gestational age*. J Pediatr Gastroenterol Nutr, 2013. **56**(5): p. 532-6.
11. Lindkvist, B., *Diagnosis and treatment of pancreatic exocrine insufficiency*. World J Gastroenterol, 2013. **19**(42): p. 7258-66.
12. Walkowiak, J., et al., *Indirect pancreatic function tests in children*. J Pediatr Gastroenterol Nutr, 2005. **40**(2): p. 107-14.
13. Soldan, W., J. Henker, and C. Sprössig, *Sensitivity and specificity of quantitative determination of pancreatic elastase 1 in feces of children*. J Pediatr Gastroenterol Nutr, 1997. **24**(1): p. 53-5.
14. Nandhakumar, N. and M.R. Green, *Interpretations: How to use faecal elastase testing*. Archives of disease in childhood - Education & practice edition, 2010. **95**(4): p. 119-123.
15. Löser, C., A. Möllgaard, and U.R. Fölsch, *Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test*. Gut, 1996. **39**(4): p. 580-6.
16. Glasbrenner, B., et al., *Clinical evaluation of the faecal elastase test in the diagnosis and staging of chronic pancreatitis*. Eur J Gastroenterol Hepatol, 1996. **8**(11): p. 1117-20.
17. Lüth, S., et al., *Fecal elastase-1 determination: 'gold standard' of indirect pancreatic function tests?* Scand J Gastroenterol, 2001. **36**(10): p. 1092-9.
18. Gelfond, D., et al., *Pancreatic Enzyme Replacement Therapy Use in Infants With Cystic Fibrosis Diagnosed by Newborn Screening*. Journal of pediatric gastroenterology and nutrition, 2018. **66**(4): p. 657-663.
19. Somaraju, U.R.R. and A. Solis-Moya, *Pancreatic enzyme replacement therapy for people with cystic fibrosis*. The Cochrane database of systematic reviews, 2020. **8**(8): p. CD008227-CD008227.
20. Sánchez, C., et al., *Breast Milk: A Source of Functional Compounds with Potential Application in Nutrition and Therapy*. Nutrients, 2021. **13**(3).
21. Lindquist, S. and O. Hernell, *Lipid digestion and absorption in early life: an update*. Curr Opin Clin Nutr Metab Care, 2010. **13**(3): p. 314-20.
22. Koh, J., et al., *Bile Salt-Stimulated Lipase Activity in Donor Breast Milk Influenced by Pasteurization Techniques*. Front Nutr, 2020. **7**: p. 552362.
23. Casper, C., et al., *rhBSSL improves growth and LCPUFA absorption in preterm infants fed formula or pasteurized breast milk*. J Pediatr Gastroenterol Nutr, 2014. **59**(1): p. 61-9.
24. Wang, Y., et al., *Transgenic mouse milk expressing human bile salt-stimulated lipase improves the survival and growth status of premature mice*. Mol Biotechnol, 2015. **57**(3): p. 287-97.
25. Strömqvist, M., et al., *Recombinant human bile salt-stimulated lipase: an example of defective O-glycosylation of a protein produced in milk of transgenic mice*. Transgenic Res, 1996. **5**(6): p. 475-85.
26. Wang, Y., et al., *Purification and characterization of recombinant human bile salt-stimulated lipase expressed in milk of transgenic cloned cows*. PLOS ONE, 2017. **12**(5): p. e0176864.

27. Fieker, A., J. Philpott, and M. Armand, *Enzyme replacement therapy for pancreatic insufficiency: present and future*. Clin Exp Gastroenterol, 2011. **4**: p. 55-73.
28. Durie, P., et al., *Diagnosis and management of pancreatic exocrine insufficiency (PEI) in primary care: consensus guidance of a Canadian expert panel*. Curr Med Res Opin, 2018. **34**(1): p. 25-33.
29. Hartmann, S., G. Rydzewska, and J.E. Domínguez-Muñoz, *Kreon(®) (Creon(®)) vs. Lipancrea(®): In Vitro Comparison of Two Encapsulated Pancreatin Preparations*. Pharmaceuticals (Basel), 2022. **15**(12).
30. Lankisch, P.G., et al., *Therapy of pancreatogenic steatorrhea: does acid protection of pancreatic enzymes offer any advantage?* Z Gastroenterol, 1986. **24**(12): p. 753-7.
31. Brock, A., et al., *Novel ciliate lipases for enzyme replacement during exocrine pancreatic insufficiency*. Eur J Gastroenterol Hepatol, 2016. **28**(11): p. 1305-12.
32. Casper, C., et al., *Recombinant Bile Salt-Stimulated Lipase in Preterm Infant Feeding: A Randomized Phase 3 Study*. PLoS One, 2016. **11**(5): p. e0156071.
33. Ziegler, J.O., et al., *Retrospective cohort analysis on pancreatic enzyme substitution in very low birthweight infants with postnatal growth failure*. Arch Dis Child Fetal Neonatal Ed, 2018. **103**(5): p. F485-f489.
34. Münch, A., C. Bühner, and A.C. Longardt, *Digestive enzyme replacement relieves growth failure in preterm infants with poor exocrine pancreatic function: a retrospective case series*. European journal of pediatrics, 2021. **180**(9): p. 2951-2958.
35. Borowitz, D.S., R.J. Grand, and P.R. Durie, *Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy*. Consensus Committee. J Pediatr, 1995. **127**(5): p. 681-4.
36. Stallings, V.A., et al., *Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review*. J Am Diet Assoc, 2008. **108**(5): p. 832-9.
37. Borowitz, D., et al., *Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis*. J Pediatr, 2009. **155**(6 Suppl): p. S73-93.
38. Ng, C., G. Major, and A.R. Smyth, *Timing of pancreatic enzyme replacement therapy (PERT) in cystic fibrosis*. Cochrane Database of Systematic Reviews, 2021(8).
39. Chauhan, S. and C.E. Forsmark, *Pain management in chronic pancreatitis: A treatment algorithm*. Best Pract Res Clin Gastroenterol, 2010. **24**(3): p. 323-35.
40. Grunert, J. and A. Tai, *Crushing pancreatic enzymes with enteral feeds in an extremely premature infant with cystic fibrosis—a novel and effective technique*. European Journal of Clinical Nutrition, 2021. **75**(1): p. 214-217.
41. Freedman, S.D., *Options for addressing exocrine pancreatic insufficiency in patients receiving enteral nutrition supplementation*. Am J Manag Care, 2017. **23**(12 Suppl): p. S220-s228.